REMARKS

1. Status

Claims 44-50 and 52-56 are currently pending, claim 51 has been canceled and claim 44 has been amended.

2. Support for Amendments

Support for the amendments to claims 44, 50, 52, and 55 can be found *inter alia* on page 87, line 10-page 88, line 9; page 88, line 10- page 89, line 3; page 89, line 4- page 90, line 3; as and page 71, line 3- page 72, line 11. No new matter has been added as a result of the instant claim amendments.

3. Priority Claim

The Action states that "priority to US Provisional Application 60/456,271, filed 3/19/2003 and 60/532,487, filed 12/26/2003, and 60/543,576, filed 2/11/2004 has been acknowledged." This information is incorrect.

As recited in the Preliminary Amendment filed with the application on October 15, 2003, "This Application is a continuation of U.S. Patent Application Serial No. 09/724,376 filed November 27, 2000, which is a divisional of U.S. Patent Application Serial No. 09/031,271 filed February 27, 1998, now abandoned, which is a continuation-in-part of U.S. Patent Application Serial No. 08/810,983, filed February 27, 1997, now U.S. Patent No. 5,989,835." Please correct the priority information to reflect the previously entered preliminary amendment.

4. Claim Objection

Claim 51 is objected to for being a duplicate of claim 50. Claim 51 has been canceled thereby obviating the objection. Applicants respectfully request reconsideration and withdrawal of the objection.

5. Rejection under 35 U.S.C. § 101

Claims 44-50 and 52-56 are rejected under 35 U.S.C. § 101 as being drawn to non-statutory subject matter. The Patent Office asserts that claim 44 recites procedures that

"are not active method steps" that "do not result in a physical transformation of matter" and therefore "encompass non-physical method steps that may be practiced inside of a computer." Applicants traverse the rejection, but have nonetheless amended the claims to obviate the rejection. Thus, Applicants respectfully request reconsideration and withdrawal of the rejection.

6. Rejections under 35 U.S.C. § 112, first paragraph

Claims 44-50 and 52-56 are rejected under 35 U.S.C. § 112, first paragraph for failing to meet the enablement requirement. The Patent Office asserts that the specification, "while being enabling for translocation between a cell nucleus and a cell cytoplasm, does not reasonably provide enablement for detecting translocation of a cellular component between any said first and second cellular compartments." Applicants traverse the rejection.

In order to meet the enablement requirement, a patent application must teach those of skill in the art how to make and use the claimed invention without undue experimentation. The factors to be considered in determining whether undue experimentation is required have been summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeal *In re Wands*, 8 USPQ2d 1400 at 1404 (CAFC 1988). As noted in M.P.E.P. 2164.01(a) "These factors include, but are not limited to: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Furthermore, M.P.E.P. 2164.01 (b) states, "As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. § 112 is satisfied. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Failure to disclose other methods by which the claimed invention may be made does not render a claim invalid under 35 U.S.C. § 112."

In the present case, the invention is in the field of cell-based screening where the level of skill in the art is high, as acknowledged by the Patent Office. The claims are not unduly broad in light of the extensive direction and working examples provided in the specification. Multiple examples of methods for detecting translocation between different cellular

compartments are recited in the specification, including specific examples of translocation between:

-Endoplasmic reticulum and the Golgi (page 71, line 3- page 72, line 11)

-Plasma membrane and cytoplasm (page 68, line 16- page 69, line 17; page 69 line 19-page 71, line 2),

-Nucleus and cytoplasm (pages 46, line 11 – page 49, line 16; page 62, line 16-page 64, line 9; page 67, line 17- page 68, line 10).

Thus, the specification provides detailed examples for detecting translocation between 5 different cellular compartments. Given the high level of skill in the art and the extensive guidance provided by the Applicants', it is thus clear that the present specification enables the full scope of the claimed invention. As recited above, "As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. § 112 is satisfied. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). As noted in MPEP 2164.01(c), "In other words, **if <u>any</u> use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention**." In the present case, the Applicants have provided much more than a single method for making and using the claimed invention, where multiple uses are disclosed. Thus, in light of all of the above, the Applicants have clearly met the enablement requirement for the presently pending claims.

In making its rejection under 35 U.S.C. § 112, first paragraph, the Patent Office appears to be requiring that, in order to meet the enablement requirement, the Applicant must limit its claims to specific details of exemplary embodiments. However, as noted in the M.P.E.P. 2164.08 (c),

> "Limiting an applicant to the preferred materials in the absence of limiting prior art would not serve the constitutional purpose of promoting the progress in the useful arts. Therefore, ***an enablement rejection based on the grounds that a disclosed critical limitation is missing from a claim should be made only when the language of the specification makes it clear that the limitation is critical for the invention to function as intended.*** Broad language in the disclosure, including the abstract, omitting an allegedly critical feature, tends to rebut the argument of criticality. "

> Furthermore, the court in *In re Goffe*, 542 F.2d 564, 567, 191 USPQ 429, 431 (CCPA 1976) stated: "[T]o provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall limit his claims to what he has found will work or to materials which meet the guidelines specified for "preferred" materials in a process such as the one herein involved would not serve the constitutional purpose of promoting progress in the useful arts."

Specifically, the Patent Office makes several specific assertions in its rejection under 35 U.S.C. § 112, second paragraph, Applicants will address these assertions with particularity as follows:

A. With respect to claim 44, the Patent Office asserts that "there is no step directed to 'detecting the translocation of a cellular component.'" As an initial matter, Applicants note that the presently pending claims are directed to "a **machine readable storage medium** comprising a program containing a set of instructions **for causing** a cell screening system **to execute procedures** for detecting the translocation of a cellular component of interest between a first cellular compartment and a second cellular compartment..." Thus, the claims will not require an **active** detection step, since the claims are reciting procedures that the machine readable storage medium **can** cause a cell screening system to execute. Furthermore, Applicants respectfully draw the Patent Office's attention to the following portion of currently pending claim 44 which clearly recites,

> "the **ratio of the intensity** of the luminescent signals from the at least second luminescent reporter molecule in the first cellular compartment mask and the second cellular organelle mask **and/or** the **difference of the intensity** of the luminescent signals from the at least second luminescent reporter molecule in the first cellular organelle mask and the second cellular organelle mask **provides a measure of the translocation of the cellular component** ..."

Thus, pending claim 44 clearly recites a step directed to procedures that the machine readable storage medium can cause a cell screening system to execute for detecting the translocation of a cellular component between different cellular compartments.

B. The Patent Office asserts that the specification discloses a method for calculating the "NucCyt Difference" and "the instant claims do not recite any such limitation." Here, the Patent Office appears to be asserting the calculating a "NucCyt difference" is a critical

feature of the claims, and thus all claims must be so limited. The Applicants traverse this assertion. As noted above,

> ***"An enablement rejection based on the grounds that a disclosed critical limitation is missing from a claim should be made only when the language of the specification makes it clear that the limitation is critical for the invention to function as intended.*** Broad language in the disclosure, including the abstract, omitting an allegedly critical feature, tends to rebut the argument of criticality." (MPEP 2164.08(c))

The specification recites several examples of broad descriptive language including page 12, line 22 through page 13, line 7, which states,

> "In another aspect of the present invention, a machine readable storage medium comprising a program containing a set of instructions for causing a cell screening system to execute procedures for defining the distribution and activity of specific cellular constituents and processes is provided...Preferred embodiments of the machine readable storage medium comprise programs consisting of a set of instructions for causing a cell screening system to execute the procedures set forth in Figures 9, 11, 12, 13, 14 or 15."

Figures 9, 11, 12, 13, 14, or 15 are flow charts which clearly outline the broad processing steps for the cell-based scanning system.

Furthermore, while the specification discloses methods for detecting translocation of a cellular component of interest between the nucleus (Nuc) and the cytoplasm (Cyt), the invention is not limited to determining translocation between only those cellular compartments. The specification provides other example of determining translocation between cellular compartments including between the endoplasmic reticulum and the Golgi (page 71, line 3- page 72, line 11) and between the plasma membrane and cytoplasm (page 68, line 16-page 71, line 2). Based on all of the above, it is clear that detecting a "Cyt-Nuc difference" is not a critical feature of the invention to which all claims must be limited.

C. With respect to claim 55, the Patent Office asserts that "it is unclear how the procedures of claim 44 are 'used to test an effect' of a test compound..." This appears to be a rejection for indefiniteness, although it appears together with the Patent Office's enablement rejection. The Applicants traverse this assertion. As discussed above, the presently pending claims are directed to "a **machine readable storage medium**

comprising a program containing a set of instructions **for causing** a cell screening system **to execute procedures** for detecting the translocation of a cellular component of interest between a first cellular compartment and a second cellular compartment..." Claim 55 recites that "the procedures are used to test an effect of a test compound on translocation of the cellular component of interest between the first cellular compartment and the second cellular compartment on or within the individual cells." Thus, it would be clear to those of skill in the art that claim 55 recites a **machine readable storage medium** comprising a program containing a set of instructions **for causing** a cell screening system **to execute procedures** for detecting the **test-compound effect on** translocation of a cellular component of interest between a first cellular compartment and a second cellular compartment..." The Patent Office asserts that "one of skill in the art would have to guess as to the type of effect that is intended by applicant." However, claim 55 plainly recites that "the procedures are used to test an effect of a test compound **on translocation of the cellular component between the first cellular compartment and the second cellular compartment on or within the individual cells**." Thus, claim 55 would be clear to those of skill in the art, and the specification provides ample examples of such test compound effects on translocation (see, for example, page 46, line 11- page 49, line 16; and Example 5, page 53, line 15- page 54, line 4).

D. With respect to claim 56, the Patent Office asserts that "the instant claims do not provide any steps for 'comparing' intensity values acquired from reporter molecules at different time points" and "one of skill in the art would have to guess what type of luminescent reporter molecules should be used." Here, the Patent Office appears to be asserting that comparing intensity values at different time points is a critical feature of the claims. Further, the Patent Office appears to be asserting that the selection of luminescent reporter molecules is not within the level of skill in the art, based on the teachings herein and the general level of skill in the art. The Applicants traverse both assertions. As noted above,

> ***"An enablement rejection based on the grounds that a disclosed critical limitation is missing from a claim should be made only when the language of the specification makes it clear that the limitation is critical for the invention to function as intended.*** Broad language in the

> disclosure, including the abstract, omitting an allegedly critical feature, tends to rebut the argument of criticality." (MPEP 2164.08(c))

The specification recites,

> "In an **alternative embodiment** of the present invention, a method of **kinetic live cell screening is provided.** The previously described embodiments of the invention are used to characterize the spatial distribution of cellular components at a specific point in time, the time of chemical fixation. As such, these embodiments have limited utility for implementing kinetic based screens, due to the sequential nature of the image acquisition, and the amount of time required to read all the wells on a plate...The **kinetic live cell extension of the invention** enables the design and use of screens in which a biological process is characterized by its kinetics instead of, or in addition to, its spatial characteristics. In many cases, a response in live cells can be measured by adding a reagent to a specific well and making multiple measurements on that well with the appropriate timing. This dynamic live cell embodiment of the invention therefore includes apparatus for fluid delivery to individual wells of the system in order to deliver reagents to each well at a specific time in advance of reading the well. This embodiment thereby allows kinetic measurements to be made with temporal resolution of seconds to minutes on each well of the plate." (page 41, line 11 through page 42, line 9)

Thus, the language of the specification does not make it clear that a limitation for comparing' intensity values acquired from reporter molecules at different time points is a critical feature of pending claim 56, but is merely an alternative embodiment.

Finally, the specification provides numerous examples and detailed disclosure on the types of luminescent molecules which can be used, including on page 15 line 21- page 16, line 3 which discloses the types of macromolecules which can be used; page 26, line 5- page 29, line 10, which discloses the types of luminescent molecules which can "used to measure the **temporal** and spatial distribution.

Based on all of the above, the Applicants respectfully request reconsideration and withdrawal of the enablement rejections.

7. Rejections under 35 U.S.C. § 112, second paragraph

Claims 44-50 and 52-56 are rejected under 35 U.S.C. § 112, second paragraph for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

35 U.S.C. § 112, second paragraph requires "the specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention."

A. The Patent Office asserts that claim 44 is indefinite in reciting "detecting translocation of a cellular component of interest," while the steps of the instant claim do not specifically require a 'cellular component of interest,' nor do they result in the 'detection' of the translocation of said cellular component of interest." Applicants traverse the rejection.

Claim 44 recites "at least a second **luminescent reporter molecule capable of reporting a cellular component of interest**." Thus, claim 44 requires luminescent molecule which reports on a cellular component of interest.

As noted above, the presently pending claims are directed to "a **machine readable storage medium** comprising a program containing a set of instructions **for causing** a cell screening system **to execute procedures** for detecting the translocation of a cellular component of interest between a first cellular compartment and a second cellular compartment..." Thus, the claims will not require an **active** detection step, since the claims are reciting procedures that the machine readable storage medium **can** cause a cell screening system to execute. Furthermore, Applicants respectfully draw the Patent Office's attention to the following portion of currently pending claim 44 which clearly recites,

> "the **ratio of the intensity** of the luminescent signals from the at least second luminescent reporter molecule in the first cellular compartment mask and the second cellular organelle mask **and/or** the **difference of the intensity** of the luminescent signals from the at least second luminescent reporter molecule in the first cellular organelle mask and the second cellular organelle mask **provides a measure of the translocation of the cellular component** ..."

Thus, pending claim 44 clearly recites a step directed to procedures that the machine readable storage medium can cause a cell screening system to execute for detecting the translocation of a cellular component between different cellular compartments. Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection.

B. The Patent Office asserts that "it is unclear whether said reporter molecules" in claim 44, step (a) "serve to define 'cellular compartment masks,' or to identify cells and report on cellular components of interest, or both." Amended claim 44 recites

> "**a plurality of luminescent reporter molecules on or in the individual cells**, wherein the plurality of luminescent reporter molecules **comprises** at least a first luminescent reporter molecule to identify the individual cells, and at least a second luminescent reporter molecule to report on a cellular component of interest, wherein luminescent signals from the at least first and the at least second luminescent reporter molecules are **optically distinguishable**..."

Thus, the claim unambiguously states that the plurality of luminescent molecules **comprise** molecules which identify individual cells and report on a cellular component of interest. The claim is clearly written to allow for multiple, **optically distinguishable** luminescent reporter molecules which can serve multiple functions. It is well within the knowledge of those with skill in the art how to use luminescent reporter molecules. Furthermore, this claim limitation is fully supported in the disclosed description of "Fluorescent Reporter Molecules" in the specification on page 26, line 4- page 29, line 10 and the working examples which disclose the use of reporter molecules. The working examples include, Example 1 which recites the use of the DNA specific fluorophore Hoechst 33423 to label nuclei and a fluorescent antibody to label a transcription factor for translocation between the nucleus and cytoplasm (page 46, line 20 – page 4,line 7); Example 7 which discloses the translocation of a GFP labeled Caspase and Hoeschst 33342 labeled nuclei (page 63, lines 6-20); and Example 9 which discloses the translocation of GFP labeled β-arrestin between various labeled organelles (page 69, line 20- page 21, line17). Claim 44 clearly points out and distinctly claims non-limiting uses of the reporter molecules as supported in the specification and thus complies with the written description requirement of 35 U.S.C. § 112, second paragraph. Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection.

C. The Patent Office asserts that claim 44, step (a), which recites a "reporter molecule to identify the individual cells" is unclear because "it is unclear is [if] this limitation is intended to be an active method step, an intended use of said reporter molecules, or otherwise." Claim 44, step (a) has been amended to recite "a first luminescent reporter

molecule **capable of identifying** the individual cells..." thereby obviating the rejection. Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection.

D. The Patent Office asserts that claim 44, step (a), which recites a "reporter molecule to report on a cellular component of interest" is unclear because "it is unclear is [if] this limitation is intended to be an active method step, an intended use of said reporter molecule, or otherwise." Claim 44, step (a) has been amended to recite "a second luminescent reporter molecule **capable of reporting** on a cellular component of interest..." thereby obviating the rejection. Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection.

8. Rejections under 35 U.S.C. § 102

Claims 45-49, 53 and 56 are rejected under 35 U.S.C. § 102 (b) as being anticipated by Kamentsky et al. (US 5,427,910). The Applicants traverse the rejection.

According to M.P.E.P. 2131, "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

As an initial matter, Applicants presume, in light of the detailed rejection which compares the cited reference with the steps of claim 44, that the Patent Office has made a typographical error in not rejecting claim **44** as well as claim 45-49, 53 and 56. Applicants have prepared their response according to this presumption.

The reference cited by the Patent Office does not teach or suggest at least the following limitations of presently pending claim 44:

> A machine readable storage medium comprising a program containing a set of instructions for causing a cell screening system to execute procedures for detecting the **translocation of a cellular component of interest between a first cellular compartment and a second cellular compartment on or within individual cells** on an array of locations which contain multiple cells, **wherein the first cellular compartment and the second cellular compartment are different, and** wherein the procedures comprise:
>
> a) **defining a first cellular compartment mask and a second cellular compartment mask** in multiple individual cells on the array of locations from luminescent signals obtained from a plurality of luminescent reporter molecules on or

in the individual cells, wherein the plurality of luminescent reporter molecules comprises at least a first luminescent reporter molecule capable of identifying the individual cells, and at least a second luminescent reporter molecule capable of reporting on a cellular component of interest, wherein luminescent signals from the at least first and the at least second luminescent reporter molecules are optically distinguishable;

b) determining an intensity of the luminescent signals from the at least second luminescent reporter molecule in the first cellular compartment mask and the second cellular compartment mask; and

c) determining one or both of the following:

i) a ratio of the intensity of the luminescent signals from the at least second luminescent reporter molecule in the first cellular compartment mask and the second cellular compartment mask; and

ii) a difference of the intensity of the luminescent signals from the at least second luminescent reporter molecule in the first cellular compartment mask and the second cellular compartment mask;

wherein the ratio of the intensity of the luminescent signals from the at least second luminescent reporter molecule in the first cellular compartment mask and the second cellular compartment mask and/or the difference of the intensity of the luminescent signals from the at least second luminescent reporter molecule in the first cellular compartment mask and the second cellular compartment mask provides a measure of the translocation of the cellular component of interest between the first cellular compartment and the second cellular compartment on or within the individual cells, and

wherein the program results are displayed to a user.

As noted in the Action, "Kamentsky et al. teach a method of fluorescent cytogenetic analysis that provides for the optical detection of chromosomal abnormalities..." Kamentsky does not teach or suggest machine readable storage medium comprising a program containing a set of instructions for causing a cell screening system to execute procedures for detecting the translocation of a cellular component of interest between a first and second cellular compartment, where the first and second cellular compartments are different.

Specifically, Kamentsky teaches

"...a method of characterizing the chromosomes in a sample of cells...by **fixing the cell sample on a substrate**, contacting the cell sample with a nucleic acid probe having a detectable label,...detecting each labeled region in the sample, assigning a position **on the substrate** to each detected labeled region... and assigning a position **on the substrate** to each region group..." in the sample,

and comparing the distance parameter for each region group to a standard distance value to characterize the chromosomes in the cells of the sample." (Column 3, lines 8-31).

The distance parameter disclosed by Kamentsky is the distance between the labeled chromosomes on the substrate, an artificial environment, not within the intact cell. Thus Kamentsky does not teach or suggest determining translocation of the labeled cellular component between organelles, as the steps recited by Kamentsky result in the destruction of the organelles. Furthermore, Kamentsky does not teach or suggest taking a ratio or a difference of the intensity of the luminescent signals as recited in claim 44. Kamentsky teaches determining the "distance between the labeled" chromosomes in order to "characterize the chromosomes in the cell sample." Finally, Kamentsky does not teach or suggest defining cellular organelle masks as recited in claim 44. Consequently, Kamentsky does not anticipate amended claim 44. Claims 45-49, 53 and 56 are dependent on claim 44 and share the above limitations, and thus Kamentsky also does not anticipate claims 45-49, 53 and 56. Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection.

9. Rejections under Obviousness Type Double Patenting

Claims 44, 50, 51, 52, 53, 55, and 56 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 4, and 8 of US Patent No. 6,671,624, issued December 30, 2003. Claim 51 has been canceled. The Applicants are herewith filing a terminal disclaimer to obviate the rejection.

Conclusion

Based on all of the above, the Applicants believe the claims are now allowable. If there are any questions or comments regarding this response, the Patent office is encouraged to contact the undersigned agent as indicated below.

Respectfully submitted,

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